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Re: Case-Control Paper

Dear Colleagues,

Here is the just published version of the case-control study of thyroid cancer in Belarus.
Lynn

Chernobyl-Related Thyroid Cancer in Children of Belarus: A Case-Control Study

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The accident at the Chernobyl nuclear power plant on April 26, 1986, released approximately 2 EBq of ¹³¹I and other radioiodine isotopes that heavily contaminated southern Belarus. An increase in thyroid cancer reported in 1992 and attributed to the Chernobyl accident was challenged as possibly the result of intensive screening. We began a case-control study to test the hypothesis that the Chernobyl accident caused the increase in thyroid cancer. Records of childhood thyroid cancer in the national therapy centers in Minsk in 1992 yielded 107 individuals with confirmed pathology diagnoses and available for interview. Pathways to diagnosis were (1) routine endocrinological screening in 63, (2) presentation with enlarged or nodular thyroid in 25 and (3) an incidental finding in 19. Two sets of controls were chosen, one matched on pathway to diagnosis, the other representing the area of heavy fallout, both matched on age, sex and rural/urban residence in 1986. The ¹³¹I dose to the thyroid was estimated from ground deposition of ¹³⁷Cs, ground deposition of ¹³¹I, a data bank of 1986 thyroid radiation measurements, questionnaires and interviews. Highly significant differences were observed between cases and controls (both sets) with respect to dose. The differences persisted within pathway to diagnosis, gender, age and year of diagnosis, and level of iodine in the soil, and were most marked in the southern portion of the Gomel region. The case-control comparisons indicate a strong relationship between thyroid cancer and estimated radiation dose from the Chernobyl accident. © 1998 by Radiation Research Society

INTRODUCTION

In children the thyroid gland is highly sensitive to the induction of cancer by radiation from external sources (1). Most cases have followed exposure of the head and neck to X-ray therapy for medical reasons (2, 3). External radiation from the atomic bombs in Hiroshima and Nagasaki also induced thyroid cancer (4). A pooled analysis of the available studies (5) yielded reasonably stable risk estimates for thyroid cancer from exposure to X and γ rays among children: an absolute risk coefficient of 4.4 excess cancers per 10,000 person-years per gray (4.4 per million per rad) and an excess relative risk of 7.7 per gray.

Comparable internal radiation exposure from the medical use of radioactive iodine (¹³¹I) has not resulted in thyroid cancer (6, 7), although few children have been studied. The exposure of Marshall Islanders to fallout from a nuclear weapons test caused thyroid cancer in children, but risk estimation for ¹³¹I is hampered by the small size of the exposed population and by the fact that perhaps 85% of the thyroid dose came from γ rays and shorter-lived radioiodine isotopes (8, 9). The latter have greater oncogenic potential than ¹³¹I in animal experiments (10).

The accident at the nuclear power plant in Chernobyl in northwestern Ukraine on April 26, 1986, released 1.5-1.9 EBq (40-50 MCi) of ¹³¹I plus other radioiodine isotopes, most of it contaminating southern regions of Belarus (11). Anticipating an increase in thyroid cancer, Soviet health authorities initiated an intensive screening program among children in areas of heavy fallout² (12). In 1992, Kazakov *et al.* (13) reported on 131 cases of thyroid cancer in children after the accident. Their distribution by time of diagnosis and geographic region of Belarus strongly suggested

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²Ministry of Health of the USSR, About medical examination of the population affected after the Chernobyl accident. Order N640, May, 1987. [in Russian]

a relationship to the accident. Most of the diagnoses had been confirmed by expert pathologists (14, 15). Concerns were expressed, however, that the increase in incidence might have resulted from intensive screening (16-18). In 1992 these concerns led us to undertake a case-control study to compare cases and controls according to estimated ^{131}I dose.

MATERIALS AND METHODS

The Cases

The 131 cases in the files of the Aksakovtchina Clinic (a national referral center) and the national thyroid surgery center at the Minsk State Medical Institute represented, in mid-1992, the entire thyroid cancer experience of children in Belarus under age 15 at the time of the accident. Deletions were made for diagnosis before 1987 (2 cases), absence from Belarus when the accident took place or in 1993-1994 when interviews were conducted (8 cases), absence of pathology information (2 cases), death (1 case) and diagnosis not reviewed or not confirmed by international pathologists or by Professor Cherstvoy, Chief, Department of Pathology, Minsk State Medical Institute (11 cases). There are 107 cases in the final case series. Various characteristics of the cases appear in Table I. The comparatively low female/male ratio (1.10) may reflect the prepubertal ages of so many of the children (19): 55 were under age 10 at diagnosis, 86 under age 10 at exposure. The earliest reports (14, 20) gave ratios of 1.2-1.3, and the most recent report (21) gives 1.5. The lesions were not trivial. Of the 5 tumors removed in 1989, at least 1 had a diameter greater than 1 cm, and the remaining 4 had invaded beyond the capsule and were comparable to those removed in 1990 or later. Among the 24 cases with known pathology detail and operated on in 1990, there was invasion beyond the thyroid capsule in 11.

Design of Epidemiological Study

Two control series were assembled in this retrospective study. The first was chosen to represent the general population of children exposed to radioiodine fallout (Type I controls). The area of Belarus was divided into an "exposure zone" (A in Fig. 1) and a much less exposed area (B). General population controls were drawn exclusively from zone A to yield a more conservative test of the null hypothesis, as 18 of the 107 cases

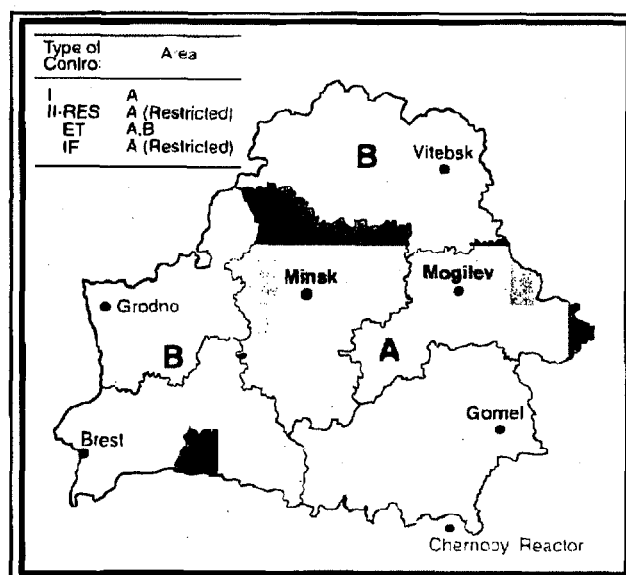


FIG. 1. Map of Belarus showing the six major civil subdivisions (oblasts) and their capitals, and distinguishing the heavy exposure zone (A) from the remainder of the country. Zone A contains about 60% of the land area of Belarus and about 65% of its population. "A (Restricted)" (not explicitly shown on the map) refers to the districts of zone A in which systematic thyroid screening had been accomplished by the time Type II controls were being selected. The three pathways to diagnosis were: RES, routine endocrinological screening; ET, enlarged thyroid; and IF, incidental finding.

TABLE I
Characteristics of the 107 Cases

1. Age at exposure (years)	5. Sex	
0-2	25 Female	56
3-5	36 Male	51
6-8	26	
9-11	20	
2. Age at diagnosis (years)	6. Pathology	105
4-6	Papillary	2
7-9	Follicular	
10-12	7. Pathology staging	15
13-16	Unclassified	
3. Region in 1986	7.1. Tumor size	
Gomel	<1 cm (T1)	23
Brest	1-4 cm (T2)	23
Mogilev	>4 cm (T3)	2
Minsk	Invasion* (T4)	44
Grodno	7.2. Lymph node metastasis	
Vitebsk	Absent (N0)	35
	Present (N1)	57
4. Rural/urban in 1986	7.3. Distant metastasis	
Rural	Absent (M0)	88
Urban	Present (M1)	4

*Beyond thyroid capsule.

originated in zone B. A total of 107 Type I controls were chosen randomly from the individual medical records in the polyclinics (facilities for preventive and outpatient medical care of the population of an area, making referrals to hospitals as needed) in each district (raion) in proportion to that district's 1986 population, not to its number of thyroid cases. The age, gender and 1986 urban/rural (or village) residence of each control were predefined to match those of a case drawn at random from among the 107 cases. The random selection avoided geographic matching which would have forced cases and controls to have had similar doses.

The second control series (Type II controls) was selected to have had the same opportunity for diagnosis as the cases (Table II). Review of the cases revealed three principal pathways to the diagnosis of thyroid cancer: (1) systematic endocrinological screening by palpation of the neck and, in some cases, by ultrasound, carried out by mobile teams visiting polyclinics or schools; (2) incidental finding during examination, e.g. a child seen in a polyclinic with an upper respiratory infection and whose physical examination revealed a possible thyroid abnormality; and (3) presentation with an enlarged thyroid, e.g. a child brought to the polyclinic because of swelling, or perhaps hardness, in the neck region that eventually led to a diagnosis of thyroid cancer. For each Type II control, the pathway to diagnosis, year of birth, gender and 1986 rural/urban residence were predefined by the same random pairing procedure that was used for Type I controls, except that the number of controls in each district was proportional to that district's population in the 1989 Soviet population census to represent more closely the population at the time active screening began. The controls for endocrinological screening and incidental finding were selected from the individual medical records of children in polyclinics in a restricted area of zone A, districts where systematic screening had been completed by the time the controls were being selected. The controls for enlarged thyroid were selected from the records of the pool of endocrinological dispensaries and/or local endocrinologists responsible for the diagnosis of the cases of enlarged thyroid, again without matching on geographic location.

TABLE II
Control Selection

Criteria	Type I General population	Type II Pathway to diagnosis		
		Routine endocrinological screening	Enlarged thyroid	Incidental finding
Geographic (Fig. 1)	Exposure zone A	Exposure zone A with mass screening ^a	Districts of enlarged thyroid cases (A, B ^b)	Exposure zone A with mass screening ^a
Medical indications ^c	—	—	Enlarged/abnormal thyroid	Respiratory symptoms leading to neck examination
Population weight	1986	1989	1989	1989
Number of controls	107	63	25	19

^aDistricts in Zone A where systematic screening had been performed by the time the controls were being selected.

^bSix were from Zone B.

^cIndividuals with known diagnoses of thyroid cancer were excluded.

Since Belarus includes areas of mild iodine deficiency which might increase absorption for radiiodine, a scale of iodine in the soil in 1970 (22) was used to classify both cases and controls. Matching on iodine was not employed, but the role of iodine in the soil was investigated during analysis.

Dosimetry

Under the constraints of the design of the epidemiological study, the same dosimetry procedure for dose estimation was to be used for all cases and controls to avoid possible biases. For that reason, data that were available for only a fraction of the subjects were ignored, and consequently, the thyroid dose estimates are more uncertain than would have otherwise been possible in those cases.

The major contribution to the thyroid dose was probably the ingestion of milk contaminated with ¹³¹I, with minor contributions from the ingestion of ¹³¹I-contaminated leafy vegetables, from the inhalation of ¹³¹I and of short-lived radioiodine isotopes (¹³²I and ¹³³I), and from external radiation from radioactive materials deposited on the ground. In addition, ingestion of mother's milk contaminated with ¹³¹I is likely to have been important for the three cases and six controls who were born in 1986.

The estimation of thyroid doses to Belarussians is based on a data bank of thyroid radioactivity measurements made within a few weeks after the accident on more than 200,000 people in the more contaminated Gomel and Mogilev regions. These measurements were used to derive the activities of ¹³¹I present in the thyroids of people at the time of measurement; in a second step, the thyroid doses received before and after the time of measurement were estimated by using personal or objective information on the relative intakes of ¹³¹I. It was assumed that a single occurrence of fallout took place after the accident and that the intake of ¹³¹I was due only to the consumption of contaminated cows' milk at a constant rate. The ingestion of leafy vegetables was not explicitly considered in the dose assessment, as the temporal variation of the ¹³¹I concentration in fresh vegetables is very similar to that in milk after a single occurrence of fallout. Inhalation of ¹³¹I was usually not considered, as the doses resulting from inhalation, when cows are on pasture, are much smaller than those due to ingestion, assuming the consumption of local milk; however, inhalation was considered for those inhabitants of rural areas who were known or suspected not to have consumed contaminated local milk or leafy vegetables as well as for the inhabitants of the city of Gomel, for whom both inhalation and ingestion were assumed to have contributed substantially to the thyroid dose. The possible intake of stable iodine for prophylactic reasons also was not taken into account. It is recognized that the uncertainties attached to both the estimation of the activity of ¹³¹I present in the thyroid at the time of measurement and the estimation of the relative intake of ¹³¹I

before and after the time of measurement are relatively large. Nevertheless, this method is at present the best that can be used to estimate individual thyroid doses. Among the individuals considered in this study, only 12 cases and no controls had been subjected to thyroid radioactivity measurements.

For villages with a sufficient number of residents with such "measured" doses, individual thyroid dose distributions were determined for several age groups and levels of milk consumption. These data were used to derive thyroid dose estimates for unmeasured inhabitants of these villages. Among the individuals considered in this study, the thyroid doses for only 55 cases and 59 controls could be estimated using this method.

Finally, for any village where the number of residents with "measured" thyroid doses is small or equal to zero, individual thyroid doses were derived from the relationship obtained between the mean adult thyroid dose and the deposition density of ¹³¹I or ¹³⁷Cs in villages with "measured" thyroid doses presenting characteristics similar to those of the village considered (23). This method can be used for any case and control as measurements of the deposition density of ¹³⁷Cs are available for all contaminated areas of Belarus.

In this study, the estimates of individual thyroid doses were made with the last method, which does not make use of all the data available but meets the criterion of being applicable to all cases and controls without introducing bias. The thyroid doses received by children were inferred from the estimated mean adult thyroid doses in the villages or towns where the persons resided, taking into account the age of the individual and his whereabouts after the accident. Information on milk consumption and on the use of agents to block absorption of radioiodine were not taken into account because they were not available for all cases and controls. Therefore, default milk consumption rates were assumed for all individuals of the same age, and it was also assumed that any intake of stable iodine for prophylactic purposes occurred too late to have had a significant effect on the thyroid dose. The contributions to the thyroid dose from external irradiation, from intake of short-lived radioiodines (¹³²I and ¹³³I) or from intake of long-lived radionuclides (¹³⁴Cs and ¹³⁷Cs) were, for most individuals, deemed to be small in comparison with the dose resulting from ¹³¹I and were not included.³

The uncertainties attached to individual thyroid doses estimated with this methodology are admittedly very large but are difficult to quantify. On the basis of thyroid dose distributions obtained in settlements

³In two dosimetry papers in preparation, the contributions to the thyroid doses from external irradiation and from intake of short-lived radioiodines as well as of long-lived radionuclides are estimated. The thyroid dose estimates obtained by the three dosimetry methods also are compared.

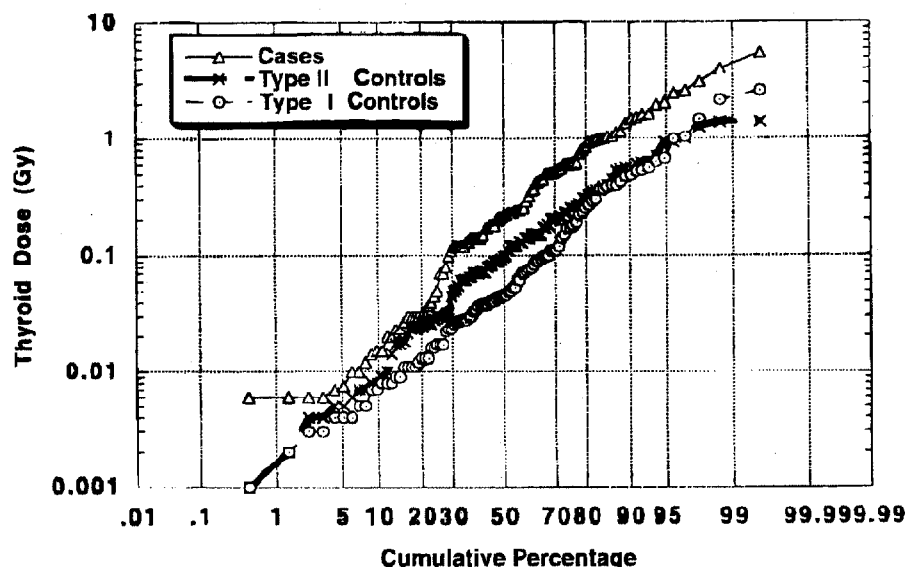


FIG. 2. Log probability plot of the individual thyroid radiation dose distributions of the cases and of the two types of controls.

with large numbers of people having thyroid measurements, it was found that the probability distribution of the derived individual thyroid doses in a settlement was lognormal with a geometric standard deviation of about 3; the corresponding 90% confidence interval ranged within a factor of approximately 6 of the best estimate. Because of these large uncertainties, it was felt desirable to assign each case or control to one of three dose categories (<0.3 , 0.3 – 0.9 and 1 Gy or more) for most analyses and to give more credibility to the assigned dose interval than to the value of the individual dose estimate. Because most of the thyroid radioactivity measurements were made in the Gomel and Mogilev regions, individual dose estimates for residents of those regions are probably less uncertain than those for residents elsewhere. Continuing dose reconstruction could lead to better estimates of individual thyroid doses and to a substantial decrease in the uncertainties associated with them.⁴

Statistical Methods

Mean values of dose were compared by analysis of variance and by t tests. Dose distributions were compared parametrically on the natural log scale and also nonparametrically with rank-based tests. The χ^2 test of homogeneity was used to compare numbers of cases and controls in the three dose groups defined above. For 2×2 comparisons, either the χ^2 test or Fisher's exact test for small cell sizes was used. Cornfield's limits are given for the 95% confidence intervals (CI) of odds ratios (OR). The OR presented here are based on the more conservative unmatched analyses that yield OR closer to one and larger P values than do the matched-pair analyses. Odds ratios, computed separately for the different levels of the covariates, were compared with Breslow's test for homogeneity. All analyses were carried out with SAS statistical software (24).

⁴The National Cancer Institute has undertaken, jointly with the Ministries of Health of Belarus and Ukraine, long-term cohort studies of thyroid disease among Belarussian and Ukrainian children who were affected by the Chernobyl accident. A criterion for selection of the cohort is that all subjects had thyroid measurements so that the dosimetric method providing the smaller uncertainties could be applied to them. Also, an important part of the studies is devoted to research related to the improvement of the thyroid dose estimates.

RESULTS

The matching of cases and controls was perfect for gender; the 5 mismatches on year of birth differed by only a single year. There were 7 mismatches on urban/rural (village) residence in Type I controls, and 11 in Type II controls.

The three main distributions of the individual estimated thyroid radiation doses are shown in Fig. 2. The distributions for both types of controls are more concentrated in the low-dose region than is the distribution of the cases. Means, [medians] and standard deviations for the three distributions, each with 107 subjects, are, in mGy: cases, 535, [220] and 848; Type I controls, 188, [46] and 386; and Type II controls, 207, [97] and 286. Both Type I and Type II control means are significantly lower ($P < 0.001$, $P = 0.003$, respectively) than that for the cases (Fig. 2). In a parametric comparison of their distributions, the two control groups differ significantly ($P = 0.04$). The difference between the two control groups probably reflects the difference between fallout levels in Zone A and its restricted area.

Table III compares cases and Type I controls in terms of the three dose intervals specified in advance of analysis. As in the comparison of mean dose, cases and controls differ significantly ($P < 0.001$), and the odds ratio for the highest compared to the lowest dose group is 5.84 with a wide confidence interval. A similarly strong relationship between dose and case/control status is found (data not shown) within year of birth, gender and year of diagnosis (before and after June 1, 1991, which divides the cases into two equal groups), and to a lesser extent within 1970 iodine level in the soil. Iodine levels in the soil, incidentally, were lower in the Gomel region than elsewhere.

Table IV gives the case-control comparison for each Type II component and for enlarged thyroid and incidental finding combined because of their small size. These comparisons,

TABLE III
Comparison of Cases and Type I Controls

	Estimated thyroid dose from ¹³¹ I (Gy)			Total	χ^2	P
	<0.30	0.30-0.99	1.00+			
Cases	64	26	17	107		
Controls	88	15	4	107		
Total	152	41	21	214	14.8	<0.001

^aOR (95% CI) 5.84 (1.96-17.3) in comparison between lowest and highest dose groups.

^bOR (95% CI) 3.11 (1.67-5.81) in comparison of <0.3 and 0.3 or more Gy.

specific to the pathway to diagnosis, also show a strong relationship between case/control status and estimated dose, with an odds ratio of 5 in the routine endocrinological screening case/control contrast between the lowest and the highest dose groups. The means, [medians] and standard deviations of the ¹³¹I dose distributions are, in mGy: for routine endocrinological screening cases and controls, respectively, 693, [250] and 980, compared to 283, [150] and 326 ($P = 0.03$ for means); and for enlarged thyroid and incidental findings combined, 309, [140] and 548 compared to 99, [30] and 166 ($P = 0.001$ for means). In the comparisons of Type II controls and cases, as in the Type I comparisons, consistent dose-related differences between cases and controls are seen within sex, year of birth and, less significantly, level of iodine in the soil. Within the intervals for dates of diagnosis, however, it is only for the later period that the Type II case-control comparison is significant ($P = 0.003$).

Within the rural/urban subgroups, the effect is seen primarily in the rural Gomel comparison. This was true in both the Type I and the Type II comparisons (Table V). Also, the dose difference between cases and controls is confined to

cases from the Gomel region (Table V). Note that 15 of the 17 high-dose cases (1 Gy or more) were of rural Gomel origin, and that there were only 4 controls with doses of 1 Gy or more, 3 of them in rural Gomel. A north/south division of Gomel reveals that the stronger relationship is in the south, the area closer to the reactor, with a highly significant OR of 19.7 compared to an OR of 2.8 for the north ($P = 0.046$), when the lowest and highest dose groups are compared. Further analysis shows that it is the rural portion of Gomel that dominates the north/south comparison.

DISCUSSION

This study makes it clear that radiation from the Chernobyl accident is responsible for the sudden and unprecedented rise in thyroid cancer among children in Belarus, especially in the Gomel region. For the purposes of this study, the estimated ¹³¹I doses need not be "true" thyroid doses; they need be only reasonable correlates of the thyroid doses from the accident, which they appear to be (23). The relationship of thyroid cancer to the Chernobyl accident is supported by earlier demographic studies (13, 25), by ecological data from Ukraine (26, 27) and by a small dose-specific case-control study in the Russian Federation (28). The short latent period, 3-4 years, may well have been influenced by the promptness with which screening of school children occurred in areas of high fallout, but further evidence of the role of the Chernobyl accident is seen in the unusually high number of thyroid cancers that have continued to accumulate over time (21). Although there can be no doubt about the role of the Chernobyl accident, there remains some uncertainty as to the role of ¹³¹I compared to other radioiodine isotopes in the fallout. The recent pooled analysis makes it abundantly clear that the thyroid gland of

TABLE IV
Comparison of Cases and Type II Controls by Type II Category

	Estimated thyroid dose from ¹³¹ I (Gy)			Total	χ^2	P	OR ^a (95% CI)	OR ^b (95% CI)
	<0.30	0.30-0.99	1.00+					
Routine endocrinological screening								
Cases	32	16	15	63	8.0	0.02	5.04	2.08
Controls	43	16	4	63	(2 df)		(1.5-16.7)	(1.0-4.3)
Incidental finding								
Cases	13	4	2	19	4.4	0.04	—	8.31
Controls	18	1	0	19	(1 df) ^c			(1.1-58)
Enlarged or nodular thyroid								
Cases	19	6	0	25	2.4	0.12	—	3.63
Controls	23	2	0	25	(1 df) ^c			(0.7-18)
Incidental finding and enlarged or nodular thyroid								
Cases	32	10	2	44	6.5	0.01	—	5.12
Controls	41	3	0	44	(1 df) ^c			(1.4-18)

^aIn contrast between lowest and highest dose groups.

^bIn contrast between lowest and the two highest dose groups.

^c1 df test is for contrast between lowest and the two highest dose groups.

TABLE V
Comparison of Cases and Controls as to Thyroid Dose, by Region and by Rural/Urban Classification

Cases/controls with estimated thyroid doses (Gy)						
	<0.30	0.30-0.99	1.00+	χ^2 (2 df)	P	OR ^a (95% CI)
From Gomel region						
Type I						
Rural	7/27	12/7	15/3	20.99	<0.001	10.42 (3.46, 31.25)
Urban	23/29	10/3	2/0	6.34	0.042	5.05 (1.27, 20)
Not from Gomel region						
Rural	14/16	3/1	0/0	1.13 ^b	0.29	3.42 (0.32, 37)
Urban	20/16	1/4	0/1	3.24 ^b	0.20	0.16 (0.02, 1.51)
From Gomel region						
Type II						
Rural	7/23	12/9	15/3	16.95	<0.001	7.41 (2.5, 21.7)
Urban	23/25	10/8	2/1	0.62	0.73	1.45 (0.52, 4.06)
Not from Gomel region						
Rural	14/16	3/1	0/0	1.13 ^b	0.29	3.42 (0.32, 37)
Urban	20/20	1/1	0/0	0.00 ^b	1.00	1.00 (0.06, 17.2)

^aIn comparisons of the lowest and the two higher dose groups combined.

^b1 df.

children is quite sensitive to the carcinogenic effect of external radiation (5), but the studies of the effects of ^{131}I in humans have lacked substantial numbers of children under age 15 at exposure, and no effect has been found in adults (6, 7). The experience of the Marshallese, where a definite carcinogenic effect of exposure to radioiodine was registered in children (8, 9), with perhaps only 15% of the thyroid dose being from ^{131}I (29), suggests that the Chernobyl effect could derive, at least in part, from radioiodine isotopes of shorter half-life and greater energy than ^{131}I . The current estimate, however, of the contribution of the short-lived radioiodines to the thyroid dose of children in Belarus is, on average, of the order of 2%, with wide variations according to the distance from the reactor site and to the mode of radioiodine intake (inhalation or ingestion). It is only among the children exposed in the Gomel region, closest to Chernobyl, that the present study shows an effect. The children of the southern part of the Gomel region are more likely to have been exposed to the shorter-lived radioiodine isotopes because of their proximity to Chernobyl. Although the Gomel region had, in 1970, significantly lower levels of iodine in the soil than other regions, the case-control differences generally persisted within iodine level in the various comparisons.

This case-control study demonstrates the need for further work if the effect of the Chernobyl accident is to be fully understood. It was not designed to explore the influence of age, gender, blocking agents, etc. A closer study is also needed of the effect of proximity to the Chernobyl plant, since children in the southern part of the Gomel region had a greater opportunity to inhale radioiodine isotopes other than ^{131}I . The evidence presented here for the relationship between thyroid cancer and the Chernobyl

accident, for the period ending mid-1992, is confined to children exposed in the Gomel region, especially in rural villages. This does not mean, however, that there is no effect outside of Gomel, since the present sample is small and lacks power with respect to the detection of an effect elsewhere. Radioiodine fallout was much heavier in the Gomel region than elsewhere in Belarus, and rural children were especially dependent on local milk sources and more often consumed milk the day of milking than did children in urban areas. Differences in sources of milk, and in access to prophylactic agents such as potassium iodide, may have played a role in the rural-urban difference. The order for iodine prophylaxis was issued by Soviet authorities late on April 30, but the distribution of potassium iodide was apparently neither uniform nor timely (30). There was systematic distribution among children evacuated from the 30-km zone starting May 5-6, but no indication that the majority of young children received stable iodine.

Could the lack of evidence of effect outside Gomel be, after all, an indication of the influence of screening, since it was in the Gomel and Mogilev regions that screening was most intensive and the IAEA study (31) in the fall of 1990 found no more nodules in contaminated areas than in uncontaminated? The IAEA study included only 323 children from contaminated areas in Belarus, Ukraine and the Russian Federation and 253 from uncontaminated areas at a time when, at most, prevalence might have been of the order of 1 or 2 per 10,000 children. It is very unlikely that screening did more than shorten the latent period, because the design of the present study controlled for intensity of screening. With the case-control approach a real dose difference should be observable at different screening levels, provided that cases and controls have been screened with

the same intensity at each level. Although routine endocrinological screening controls could not be obtained from the actual lists of routinely screened children from which the screening cases emerged, they were selected from districts in which thorough screening had been performed by endocrinologists, often with the aid of ultrasound, by the time the controls were chosen. Comparison of enlarged thyroid and incidental finding cases and their controls provides independent dose-specific evidence of the relationship to the Chernobyl accident. Additional evidence is that the number of cases has continued to increase well into 1997 and only in children who were alive or *in utero* at the time of the accident (32, 33). Furthermore, a majority of the cancers were larger than 1 cm or had spread beyond the thyroid capsule, and 62% had metastasized to regional lymph nodes, characteristics that distinguish them from occult cancers (14, 15).

The odds ratios calculated from the case-control comparisons are indicative of a strong relationship between radiation dose and the development of thyroid cancer. Although the follow-up of patients exposed to diagnostic doses of ^{131}I has thus far failed to show an increased risk of thyroid cancer (6, 7), the experience of children exposed to fallout from the Chernobyl accident raises the possibility that very young children may indeed be at risk. Dose refinement and the prospective study of a large cohort of those children who had thyroid radioactivity measurements in 1986 should yield much-needed quantitative information on the risk from exposure to the radioiodine isotopes and, hopefully, to ^{131}I itself.

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REFERENCES

1. R. E. Shore, Issues and epidemiologic evidence regarding radiation-induced thyroid cancer. *Radiat. Res.* **131**, 98-111 (1990).
2. R. E. Shore, L. H. Hempelmann and E. D. Woodard, Carcinogenic effects of radiation on the human thyroid gland. In *Radiation Carcinogenesis* (A. C. Upton, R. E. Albert, F. Burns and R. E. Shore, Eds.), pp. 293-309. Elsevier, New York, 1986.
3. A. B. Schneider, E. Shore-Freedman, U. Y. Ryo, C. Beckerman, M. Favus and S. Pinsky, Radiation-induced tumors of the head and neck following childhood irradiation. *Medicine* **64**, 1-15 (1985).
4. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochkubo, S. Sugimoto, T. Ikeda, M. Terasaki, S. Izumi and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958-1987. *Radiat. Res.* **137** (Suppl.), S17-S67 (1994).
5. E. Ron, J. H. Lubin, R. E. Shore, K. Mabuchi, B. Modan, L. Pottern, A. B. Schneider, M. A. Tucker and J. D. Boice, Jr., Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. *Radiat. Res.* **141**, 259-277 (1995).
6. L.-E. Holm, K. E. Wiklund, G. E. Lundell, N. A. Bergman, G. Bjelkengren, E. S. Cederquist, U. B. C. Ericsson, L. G. Larsson, M. E. Lidberg, R. S. Lindberg, H. V. Wicklund and J. D. Boice, Jr., Thyroid cancer after diagnostic doses of iodine-131: A retrospective cohort study. *J. Natl. Cancer Inst.* **80**, 1132-1138 (1988).
7. P. Hall, A. Mattsson and J. D. Boice, Jr., Thyroid cancer after diagnostic administration of iodine-131. *Radiat. Res.* **145**, 86-92 (1996).
8. J. Robbins and W. Adams, Radiation effects in the Marshall Islands. In *Radiation and the Thyroid* (S. Nagataki, Ed.), pp. 11-24. Excerpta Medica, Amsterdam, 1989.
9. E. T. Lessard, A. B. Brill and W. H. Adams, Thyroid cancer in the Marshall Islands: Relative risk of short-lived internal emitters and external radiation exposure. In *4th International Radiopharmaceutical Dosimetry Symposium* (A. Shlafke-Stelson and E. Watson, Eds.), pp. 628-647. CONF-85113, National Technical Information Service, Springfield, VA, 1985.
10. NCRP, *Induction of Thyroid Cancer by Ionizing Radiation*. Report No. 80, National Council on Radiation Protection and Measurements, Bethesda, MD, 1985.
11. U.S. Nuclear Regulatory Commission, *Report on the Accident at the Chernobyl Power Station*. NUREG-1250, U.S. Government Printing Office, Washington, DC, 1987.
12. L. N. Astakhova, Thyroid system state and peculiarities of pathology formation in population of BSSR affected by radionuclides of iodine following the Chernobyl accident. *Pub. Health Belarus* **N6**, 11-16 (1990). [in Russian]
13. V. S. Kazakov, E. P. Demidchik and L. N. Astakhova, Thyroid cancer after Chernobyl. *Nature* **359**, 21 (1992). [letter]
14. A. W. Furmanchuk, J. I. Averkin, B. Egloff, C. Ruchti, T. Abelin, W. Schappi and E. A. Korotkevich, Pathomorphological findings in thyroid cancers of children from the Republic of Belarus: A study of 86 cases occurring between 1986 (post-Chernobyl) and 1991. *Histopathology* **21**, 401-408 (1991).
15. K. Baverstock, B. Egloff, A. Pinchera, C. Ruchti and D. Williams, Thyroid cancer after Chernobyl. *Nature* **359**, 21-22 (1992). [letter]
16. V. Beral and G. Reeves, Childhood cancer in Belarus. *Nature* **359**, 680-681 (1992). [letter]
17. I. Shigematsu and J. W. Thiessen, Childhood thyroid cancer in Belarus. *Nature* **359**, 681 (1992). [letter]
18. E. Ron, J. Lubin and A. B. Schneider, Thyroid cancer incidence. *Nature* **360**, 113 (1992). [letter]
19. H. R. Harach and E. D. Williams, Childhood thyroid cancer in England and Wales. *Br. J. Cancer* **72**, 777-783 (1995).
20. E. D. Cherstvoy and A. M. Necrovia, Morphologic characterization of thyroid carcinomas in children of the Republic of Belarus. In *Treatment of Thyroid Cancer in Childhood* (J. Robbins, Ed.), pp. 41-44. DOE/EH-0406, U.S. Department of Energy, Washington, DC, 1994.
21. E. P. Demidchik, I. M. Drobyshvskaya, E. D. Cherstvoy, L. N. Astakhova, A. E. Okeanov, T. V. Vorontsova and M. Germenchuk, Thyroid cancer in children in Belarus. In *Proceedings of the First International Conference of the European Community, Belarus, the Russian Federation, and Ukraine on the Radiological Consequences of the Chernobyl Accident*, Minsk, 1996, pp. 677-682. EUR 16544, European Commission, Luxembourg, 1996.
22. Belarussian State University, *Micro Elements, BSSR, and Microfer tilization's Effectiveness*. Minsk, Belarus, 1970. [in Russian]

23. Y. Gavrilin, V. Khrouch, S. Shinkarev, V. Drozdovitch, V. Minenko, E. Shernyakina, A. Bouville and L. Anspaugh. Estimation of thyroid doses received by the population of Belarus as a result of the Chernobyl accident. In *Proceedings of the First International Conference of the European Community, Belarus, the Russian Federation, and Ukraine on the Radiological Consequences of the Chernobyl Accident*, Minsk, 1996, pp. 1011-1020. EUR 16544, European Commission, Luxembourg, 1996.
24. *SAS User's Guide: Statistics, Version 5*. SAS Institute, Cary, NC, 1985.
25. T. Abelin, J. I. Averkin, M. Egger, B. Egloff, A. W. Furmanchuk, F. Gurtner, J. A. Korotkevich, A. Marx, I. I. Matveyenko and A. E. Okeanov. Thyroid cancer in Belarus post-Chernobyl: Improved detection or increased incidence? *Soz Pravitimed*. **39**, 189-197 (1994).
26. I. A. Likhtaryov, B. G. Sobolev, I. A. Kairo, N. D. Tronko, T. I. Bogdanova, V. A. Oleinic, E. V. Epshtein and V. Beral. Thyroid cancer in the Ukraine. *Nature* **375**, 365 (1995). [letter]
27. B. Sobolev, I. Likhtaryov, I. Kairo, N. Tronko, V. Oleynik and T. Bogdanova. Radiation risk assessment of the thyroid cancer in Ukrainian children exposed due to Chernobyl. In *Proceedings of the First International Conference of the European Community, Belarus, the Russian Federation, and Ukraine on the Radiological Consequences of the Chernobyl Accident*, Minsk, 1996, pp. 741-748. EUR 16544, European Commission, Luxembourg, 1996.
28. V. K. Ivanov, A. F. Tsyb, Ye. G. Matveenkov, Ye. M. Parshkov, M. A. Maksyutov, A. I. Gorskiy, V. A. Pitkevitch, V. F. Stepanenko, Ye. M. Rastopchin, A. M. Korelo, S. Yu. Chekin, I. K. Khvostunov, V. V. Shakhhtar, V. F. Gorobets, V. A. Matyash, V. A. Sevan'kaev, V. B. Ryvkin, A. D. Proshin, V. V. Dorokhov, B. K. Litvinov, B. I. Kvitko, S. Yu. Leshakov, V. A. Efendiev, M. P. Borovikova and V. I. Shiryaev. Preliminary assessment of the radiation risks of thyroid cancer in children and adolescents of the Bryansk Region according to case-control technology. In *Bulletin of the National Radiation and Epidemiological Registry Moscow-Obninsk: Special Issue 95/1, Radiogenic Thyroid Cancer*, Pt. 3, pp. 25-29, 1995. [in Russian]
29. E. Lessard, R. Miltenberger, R. Conard, S. V. Musolino, J. R. Naidu and A. Moorthy. *Thyroid Absorbed Dose for People at Rongelap, Utirik, and Sifo on March 1, 1954*. BNL-51882, Brookhaven National Laboratory, Upton, NY, 1985.
30. F. A. Mettler, H. D. Royal, J. R. Hurley, F. Khafagi, M. C. Sheppard, V. Beral, G. Reeves, E. L. Saenger, N. Yokoyama, V. Parshin, E. A. Griaznova, M. Taranenko, V. Chesin and A. Cheban. Administration of stable iodine to the population around the Chernobyl nuclear power plant. *J. Radiol. Prot.* **12**, 159-165 (1992).
31. F. A. Mettler, M. R. Williamson, H. D. Royal, J. R. Hurley, F. Khafagi, M. C. Sheppard, V. Beral, G. Reeves, E. L. Saenger, N. Yokoyama, V. Parshin, E. A. Griaznova, M. Taranenko, V. Chesin and A. Cheban. Thyroid nodules in the population living around Chernobyl. *J. Am. Med. Assoc.* **268**, 616-619 (1992).
32. D. V. Becker, J. Robbins, G. W. Beebe, A. Bouville and B. W. Wachholz. Childhood thyroid cancer following the Chernobyl accident: A status report. *Endocrinol. Metabol. Clin. N. Am.* **25**, 197-211 (1996).
33. E. D. Williams, E. Cherstvoy, B. Egloff, H. Höfler, G. Vecchio, T. Bogdanova, M. Fragarik and N. D. Tronko. Interaction of pathology and molecular characterization of thyroid cancers. In *Proceedings of the First International Conference of the European Community, Belarus, the Russian Federation, and Ukraine on the Radiological Consequences of the Chernobyl Accident*, Minsk, 1996, pp. 699-714. EUR 16544, European Commission, Luxembourg, 1996.